

Does Chinese Herbal Medicine Really have Hepatotoxicity? ---An In-Depth Analysis Based on a Large Number of Literatures May Reveal Some of the Truth

Lifang He, Yingzhe Lu, Ru Li, Jing Sun and Shaoquan Xiong*

Hospital of Chengdu University of Traditional Chinese Medicine, China

***Corresponding author:** Shaoquan Xiong, Hospital of Chengdu University of Traditional Chinese Medicine, NO.39 Shi-er-qiao Road, Chengdu, Sichuan Province, P.R. China, Postal Code : 610072, Tel: 18780293171; E-mail: xsquan106@163.com

Abstract

Chinese herbal medicine (CHM), a special drug applied under the guidance of the unique theory of Chinese medicine, in the past few decades, with its gradual application in the world, attracts many researchers to explore its clinical safety, especially CHM is considered to have hepatotoxicity, which has aroused widespread controversy. Though many reports suggest that certain herbal medicines can cause liver damage, many scholars of CHM have raised doubts because this is quite different from what most Chinese medicine practitioners perceive in clinical practice and the feedback after the patient's medication.

Objective and methods: In order to further analyze its clinical safety objectively and impartially, we consulted a large number of literature and adverse reaction reports.

Results: found that many reports were flawed in method or theory: case information was incomplete; the use of overdosing ultra-therapeutic, hyper-adaptations by patients or doctors; the model of clinical patients with inappropriate animals for basic laboratory research, most importantly, to completely break away from the theory of CHM, and so on.

Conclusions: Therefore, this article based on a large number of literature reports will contribute to a fairer and objective understanding of the clinical safety of CHM.

Keywords: Chinese herbal medicine; Hepatotoxicity; The literature

Abbreviations: CHM: Chinese Herbal Medicine; TCM: Traditional Chinese Medicine; CNKI: The China National Knowledge Infrastructure; NMPA: National Medical Products Administration; HILI: Herb Induced Liver Injury

Background

The theory of Traditional Chinese Medicine (TCM) has accumulated thousands of years of practical experience of doctors, and its modern clinical application is becoming more and more extensive. The course of some chronic diseases such as diabetes, coronary heart disease, hypertension, etc., is long and more complications, although western medicine can quickly relieve some symptoms, long-term use will produce drug resistance or liver and kidney damage. Patients of these chronic diseases [1-3] choose Chinese medicine, not only to alleviate symptoms but also to fundamentally improve the body's function, thus really conducive to the cure of disease relief. Meanwhile, emotional diseases such as anxiety disorders [4], depression [5], can obviously benefit from traditional Chinese medicine formula treatment with a significant recovery effect. In addition, in a certain stage of cancer treatment, Chinese medicine not only can prevent tumorigenesis, reduce the toxicity of chemotherapy, and improve the effectiveness of treatment, but also reduce tumor recurrence and metastasis [6]. In particular, in the current prevention and control of the new crown epidemic, Chinese medicine has also shown outstanding therapeutic effect, which can reduce acute lung injury, shock resistance, and enhance lung function [7]. As mentioned above, Chinese herbal medicine has achieved satisfactory results in the treatment of many clinical diseases, but in recent years, some reports based on western medicine pharmacology concluded that herbal medicine has hepatotoxicity, even completely deny the clinical value of Chinese medicine, such as: coptis [8]. Coptis was once widely used in some diseases, such as heart-burning oral ulcers, but there are also reports that claiming it has liver injury characteristics, which makes us Chinese medicine practitioners have to explore these reports objectively and impartially. This paper reviewed a large number of literature reports and adverse reaction reports of the NMPA, found that aloe [9], Polygoni multiflora [10], Qubaibabuqi [11] and other once widely used herbs caused liver injury after using. This is not conducive to the rehabilitation of human diseases, but also not conducive to the academic development of Chinese medicine. Therefore, this paper further in-depth analysis of these literatures or reports.

Research Methods

To search In PubMed, CNKI and NMPA adverse reaction report information communication, in order to prevent the leakage of some of the literature named after the drug, we do not use "Chinese medicine, herbal medicine" restrictions, only "hepatotoxicity, liver injury" combined with "drugs", take side-by-side relationship settings, and search with topics or abstracts, selecting 2016.1.1 to 2020.12.31, excluding literature reviews, critical article, as a result, collected 11,190 literatures and reports. Among them, there are 484 literatures related to CHM. excluding western medicine or other literatures related to liver damage unrelated to CHM. These documents include 389 domestic reports, 95 foreign literatures, 329 reports based on basic experiments, 155 from clinical reports, 106 retrospective clinical studies in clinical reports. In all such reports, Chinese medicine or natural herbal monosome tablets accounted for 87, Chinese traditional medicine 68, Chinese medicine extraction ingredients related to 329 which does not include 106 clinical retrospective studies involving drugs, because most retrospective studies don't fully list the relevant drugs suspected of liver damage. In the 77-phase adverse reaction report communication of NMPA, 25 kinds of Chinese herbal medicine were involved, including 12 cases of herbal medicine-related injection preparations and 5 cases of Chinese and western medicine mixed preparations **Table 1 and 2.**

Table 1: Different types of TCM related literature classification. (The data are from CNKI, PubMed database).

Category	Quantity (number of documents)	Literature count	Examples of documents
Domestic report		389	Psoralen [12], bupleurum [13]
Foreign reports		95	red bush tea [14], KAVA [15], Artemisia annua Tea [16]
Laboratory research		329	Aloe [17], Dictamni [18], rhizoma paridis [19]
Clinical case		155	turmeric [20], lian-sepent [21], Garcinia cambogia [22]
TCM monolithic decoction pieces		87	Elimination tablets [23], Niu Huang Jiedu Tablet [24]
Chinese patent medicine		68	Emodin [25], Tripterygium wilfordii [26], Psoralen [27]
TCM Extracted Ingredients		329	
In Clinical case		Medication time <1 month 31	
		Medication time >1 month 36	

Table 2: Classification of different types of TCM related adverse reactions reports. (The data are from adverse reaction report of NMPA).

Category	Quantity (number of documents)	Literature count	Examples of documents
Altogether consulted		77	
TCM monolithic decoction pieces		25	Pueraria lobata, Aristolochia
Injection preparation		12	Safflower injection, Shengmai injection
Chinese patent medicine		10	Longdan Xiegan Decoction, Zhuanggu joint pills
Chinese and Western medicine compound preparations		5	Ganmaoqing Capsules, Zhenju Antihypertensive Tablets

Herb medicine is applied under the guidance of Chinese medicine theory, not modern pharmacology or ingredients

First of all, it should be clear that Chinese herbal is not completely equivalent to natural plants, but a medicine that is used after dialectic, selection, reasonable processing and combination under the guidance of TCM theories. Herbs has partiality, that is, four properties and five tastes and other attributes: cold and hot, warm, bitterness, sweetness. It is the partiality that can correct the disease state of internal environment imbalance. If with no such partiality, there will be no difference between Chinese herbs and edible natural plants. In addition, Chinese medicine pays attention to correcting deviations, such as treating cold syndrome with hot natured drugs

and treating hot syndrome with cold natured drugs, so as to achieve the goal of internal environment balance and disease alleviation. If it is not used in this way, it can no longer be called CHM in a sense. Therefore, the damage of body function caused by such wrong using cannot be one-sidedly concluded that Chinese herbs has hepatotoxicity. For example, Rhizoma Coptidis can clear away heat and detoxify, and is often used to treat oral ulcers of heat-toxic type. Western medicine believes that Coptis has anti-inflammatory and antibacterial effects, but Chinese medicine believes that the guiding theory is that treating hot syndrome with cold natured drugs. In fact, there are often some oral ulcers in clinic, which are syndrome of true cold disease with false heat manifestation. At this time, they can be used under the theory of western medicine, but the results are often counterproductive and even cause body function damage. Re-entry another example, floating wheat and wheat, which the main ingredients are protein and starch, have the same source under the theory of western medicine, but under the theory of Chinese medicine, floating wheat has the property of lifting and buoyancy, which can treat night sweats, while wheat cannot. However, there have been many reports (as shown in the table) explore the clinical safety of herbs medicines completely break away from the theory of TCM but blindly rely on the pharmacological theories and component analysis, even directly isolates and extracts chemical components from herbs in the laboratory. These does not conform to the theory and clinical practice of CHM. How controversial! It should be clear that CHM is a complex composed of multiple components, and its medicinal effect is the comprehensive effect of multiple ingredients. Even if it is a single herb decoction piece, the effects of multiple ingredients in it are mutually restricted and synergistic, so, overemphasis on the hepatotoxicity of a single component is unscientific. The hepatotoxicity of emodin is not equivalent to the hepatotoxicity of Polygonum multiflorum. Moreover, in clinical practice, many Chinese herbs are not excavated and dried to use, but need to be processed rationally. After roasting and simmering, whether their pharmacological components will change remains to be further studied. In addition, herbs are rarely used alone, but combined to achieve the purpose of enhancing the efficacy and reducing side effects. After compatibility, the various components will inevitably change. For example, Sini Decoction is in the process of suffering the licorice carboxylic acid chemically reacts with the alkaloids in the aconite, thereby reducing the adverse reaction of the aconite [28]. Therefore, the pharmacological research results of isolating and extracting toxic components cannot be equal to a certain herb, let alone the effect of a certain prescription. The traditional toxicity separation procedure ignores the synergistic and detoxication effects of multiple components of CHM.

TCM pays attention to syndrome differentiation and treatment, pursuing non-toxic and effective treatment

According to the time of liver injury in the literature or reports, adverse reactions can be divided into chronic liver injury and acute liver injury. The former is mostly caused by over-treatment and excessive accumulation of drugs in the body; the latter is mostly because of individual differential reactions-- allergic reaction or high-dose use of use. During treatment, it is important to discover problems and adjust medication in time based on the patient's symptoms and signs after medication. However, symptoms, a reflection of the dynamic process of disease occurrence and development, are not static. Therefore, every herb and every prescription is only suitable for the current disease type but not beyond the course of treatment. In many adverse reaction reports, patients bought and took Qubaibabuqi tablets by themselves for 7 months [29], took Guanxinsuhe pills containing aristolochic acid for 2 years, and took Longdanxiegan Decoction for 2 years (the case was from the NMPA).

What a security risk! In clinical practice, Longdan Xiegan Decoction, of bitter-cold nature, is used to clear liver and gallbladder fire or damp-heat away, such as hepatitis, cholecystitis, insomnia dreaminess, and diarrhea, etc., which should discontinue medication as soon as get effect, that is, stop the decoction when the signs or symptoms are relieved. There are also some patients who have used it in a short period of time or even failed to achieve the therapeutic effect for the first time and have side effects. According to the pursuit of non-toxicity in traditional Chinese medicine, it should be adjusted in time to make the drug more in line with the condition. Then why do side effects occur? It is summarized as follows: 1. Individual differences, namely allergic reactions, are not ruled out; 2. The level of some doctors is different, because they are not accurate enough to understanding the nature of the disease, so that the medicine is not symptomatic or the medicine is not proficient enough, so that cause overdose or over course of medication. 3. It is common for patients to buy and take CHM without a prescription or not following the doctor's advice. In fact, there is a subtle relationship between hepatotoxic and liver protection. Some studies believe that some herbs have two-side potential, that is, switching between hepatotoxicity and liver protection depends on the dose and state of the body. For example, rhubarb [30] exhibits liver protection at low doses but can cause liver damage at high doses. However, over-dose, over-treatment, and over-indication medication have violated the tenet of CHM. TCM clinical practice pays attention to dialectical correction, which is a dynamic process that will be adjusted at any time according to the patient's current condition.

Herbs vary in quality and have no prescription restrictions

Many of the searched documents are domestic western medicine or foreign reports (as the table above). Whether these doctors are proficient in the theory of TCM and herbal property, is not clear. Regarding different reports, due to different cultivated climate and geological conditions, the quality of herbs have yet to be studied, such as the case of American Baifang [31], the case of Korean white fresh peel [32], and the case of Taiwan octagonal lotus [33]. The study data for different regions only belong to the medicinal materials under the background of local, which are not completely consistent with TCM theories, and even in a sense can no longer be called CHM. In many cases, the composition, source, dosage, quality test, and detection of harmful substance contamination of CHM that may cause liver damage are not well recorded, and the lack of quality testing of herbs that because liver damage is also an important reason for misdiagnosis of HILI (Herb-Induced Liver Injury). Due to unreasonable publicity of herbs, improper management and control of regulatory authorities, and patients lack of prescription awareness, in fact, it is very common for individuals to purchase certain herbal medicines as food supplements without a doctor's direct prescription. Some patients don't have awareness of prescriptions and use Kratom-containing herbs [34] by their own. What's more, some use herbs containing *Garcinia cambogia* [35] as dietary supplements to promote weight loss. These both are lack of doctor's dialectical treatment and prescription restrictions. Clinically, it should be ensured that the prescription is written by a doctor who has obtained the TCM license and certification. Each herb has certain indications, specific usage and dosage, and adverse reactions caused by exceeding the maximum dosage without following the doctor's advice can no longer be called TCM to a certain extent. These are the main problems that lead to exaggerated Chinese medicine liver damage [36].

How significant the basic research on herbal hepatotoxicity for clinical guidance of traditional Chinese herbs is?

As mentioned earlier, TCM should be applied under the guidance of the basic theories of TCM rather than according to the physical ingredients of western medicine. However, most of the literatures on liver damage such as Polygonum multiflorum [37], Tripterygium wilfordii [38], and Sophora flavescens [39] (the above table) are based on laboratory research data. Blindly following the research model of western medicine, using normal animals or in vitro cells as the carrier of TCM research is flawed [40]. This is not in line with the clinical practice of TCM, and the conclusions drawn are not scientific. why? First of all, although humans and mice are 95% genetically identical, the remaining 5% makes humans and mice have a huge difference. Secondly, using a healthy mouse model to simulate patients who required drug intervention in clinical are not comparable. For example, the cold and cool Zhi Zi Hou Pu Decoction [41] is applied to healthy rats, it will inevitably break the original balance and cause damage to the body. However, it will not be used for people in non-disease states in clinical practice. Moreover, studies have shown that healthy rats and diseased rats have a differential response to Rhubarb [42]: it can induce liver damage in normal rats, but it fails to induce hepatotoxicity in a rat model of liver fibrosis. The adverse reactions, and even toxicity, obtained by giving TCM to healthy rats can only belong to the data of healthy rats not clinical patients. There are also studies that take this into account and adopt modelling, but some modelling methods are also flawed: standard cells are used to create models and then injected subcutaneously to form tumor-carrying mice [43]. However, the occurrence and development of human diseases, especially the occurrence and development of tumors, are the results of many factors such as diet, emotions, climate, and life, which is even more intricate and cannot be simulated by subcutaneous injection of tumor cells like modelling. Moreover, emotions have a non-negligible impact in the development of diseases. The anger, joy, sorrow, and fear cannot be simulated in animal models. In addition, the most important thing for TCM is to communicate with patients and then adjust medication, but which cannot be achieved in basic experiments. Therefore, we believe that although many basic research reports of HILI are true, they are of little significance for clinical guidance of Chinese medicine. It must be mentioned that the TCM syndrome type cannot be simulated on the animal model in the laboratory. Polygonum multiflorum, nourishing liver and kidney, strengthening muscles and bones, nourishing blood and other benefits, is clinically used for middle-aged and elderly patients with deficiency of kidney yin and kidney essence. However, the mice selected in laboratory research often are healthy or young with weak spleen and stomach. In addition, many studies have not ruled out or reviewed the influence of laboratory conditions on the model after obtaining suspected liver damage samples, such as laboratory temperature, humidity, lighting time, and cleanliness of bedding.

Lack of detailed medical record information

Diagnostic criteria and observation indicators: In clinical case reports of HILI, there is a lack of exact and uniform diagnostic criteria, and the exclusive diagnosis is mostly used. In some cases, patients used Isotretinoin [44] as a supplement during the herbal treatment process, which is no exact diagnosis basis and exclusion criteria, for example, liver damage caused by viral, alcoholic, immune and other reasons; lack of detailed biochemical diagnostic criteria; in addition, fake and inferior CHM products or pesticides, soil-specific impurities, etc., that may remain in the medicinal materials. What's more, the collection of medical history is mainly based on the oral statements of patients without medical background, which lacks objective authenticity.

Moreover, the observational indicators in the laboratory are temporary, variable, and unpredictable. For example, elevated ALT is not a specific indicator of liver damage, but also raised in myocardial and skeletal muscle diseases. Furthermore, factors other than drugs and diseases are not taken into consideration, for instance, staying up late, insomnia, and strenuous exercise should be excluded.

The establishment of causality: Most of the clinical cases we have consulted are retrospective clinical studies, which are not sufficiently scientific and are greatly affected by subjective factors. They are prone to selection bias and recall bias. The sample size is limited, and the order in which they appear of exposure and disease is often difficult to judge. Some 106 retrospective clinical studies only simply recorded the results of the study, without detailed diagnostic criteria, inclusion criteria, and exclusion criteria. The causal relationship between the use of herbal medicine-related preparations and liver injury is blurred. For example: patients with glioblastoma not only had used Chinese herbal formula Buzhong Yiqi Pill [45], but also had used the chemotherapy drug temozolomide; patients with lung cancer were taking budesonide and sitalipine during the period, while using of several natural herbal medicines for self-treatment [46]. These have neither detailed prescription information nor specific medication details. Neither the relevant biochemical indicators changes caused by the occurrence and development of the tumor itself nor the influence of other radiotherapy and chemotherapy methods are excluded. Therefore, some cases cannot be incorporated into HILI blindly. In addition, there is overlap between some databases of clinical cases found on PubMed and the same author has duplicate publications in different journals, which leads to a certain controversy over the large proportion of HILI. A large number of reports have exaggerated the HILI, and its clinical value and scientific significance need further investigation. In addition, in the process of our literature review, there are also 2009 articles argued that the advantages of herbal medicine outweigh the disadvantages, even that some herbs do not have liver damage but have hepatoprotective effects, most of which are licorice [47] and turmeric [48].

Summary

To sum up, herb medicine, the substances that can be used to treat clinical diseases after reasonable preparation and compatibility only under the guidance of the basic theories of TCM, is not equal to natural plants. If used incorrectly and unreasonably, such as using guided by the theory of chemical ingredients, the CHM is inevitable to cause unnecessary body damage, but this can no longer be called CHM to a certain extent, so it cannot be incorporated into HILI blindly. In clinical practice, it is often known that some western medicines have liver and kidney damage, but because of no other choice, clinical practitioner of western medicine have to use them, such as anti-tuberculosis drugs, which is slightly different from herb medicine. TCM not only has a wide range of varieties, but also can be processed and compatible to achieve the purpose of reducing toxicity and increasing efficacy. If components of herb medicine are not therapeutic ingredients, they should be directly removed when preparing the medicinal materials; if are, they will be processed and choose compatibility. The toxic components of cinnabar are soluble in water, and repeated levigating grinding in water during preparation to reduce toxicity [49]. Even though some herbs have obvious side effects when used alone, they are rarely used alone in clinical practice, but choose compatibility, for example, Ginger inhibits the toxicity of tuber Pinellia [50]. In general, it can be seen that there are many controversies in the literature reporting on HILI, so Chinese herbs should be treated objectively and scientifically, and should not be denied blindly. Some Chinese medicines to treat certain diseases have a history of thousands of years in China, so it must be of clinical value to be inherited and applied.

In all clinically reported cases, excluding factors such as the quality of herb medicine, the patient's internal immunity, and the doctor's dialectical medication misapplication, most of the liver damage of TCM is caused by unreasonable and incorrect application. Therefore, in clinical practice, the four properties and five tastes and processing, compatibility and detoxification of TCM should be understood and mastered strictly under the theoretical guidance of TCM.

References

1. Wang QH, Gai LJ. Clinical efficacy observation of traditional Chinese medicine in the differentiation treatment of type 2 diabetes mellitus with hyperlipidemia. *Clin J Chin Med*. 2020;12(36):60-62.
2. Ren FW, Lin WQ. Research progress on treatment of primary hypertension in TCM. *Heilongjiang J Tradit Chin Med*. 2020;49(02):47-48.
3. [Li L, Zhou X, Li N, Sun M, Lv J, Xu Z. Herbal drugs against cardiovascular disease: traditional medicine and modern development. *Drug Discov Today*. 2015;20\(9\):1074-86.](#)
4. [Chi X, Wang S, Baloch Z, Zhang H, Li X, Zhang Z, et al. Research progress on classical traditional Chinese medicine formula Lily Bulb and Rehmannia Decoction in the treatment of depression. *Biomed Pharmacother*. 2019;112:108616.](#)
5. [Zhang K, Yang J, Wang F, Pan X, Liu J, Wang L, et al. Antidepressant-like effects of Xiaochaihutang in a neuroendocrine mouse model of anxiety/depression. *J Ethnopharmacol*. 2016;194:674-83.](#)
6. [Ling CQ, Yue XQ, Ling C. Three advantages of using traditional Chinese medicine to prevent and treat tumor. *J Integr Med*. 2014;12\(4\):331-5.](#)
7. [Zhao Z, Li Y, Zhou L, Zhou X, Xie B, Zhang W, et al. Prevention and treatment of COVID-19 using Traditional Chinese Medicine: A review. *Phytomedicine*. 2020; 20:153308.](#)
8. [Efferth T, Schottler U, Krishna S, Schmiedek P, Wenz F, Giordano FA. Hepatotoxicity by combination treatment of temozolomide, artesunate and Chinese herbs in a glioblastoma multiforme patient: case report review of the literature. *Arch Toxicol*. 2017;91\(4\):1833-46.](#)
9. [Quan Y, Gong L, He J, Zhou Y, Liu M, Cao Z, et al. Aloe emodin induces hepatotoxicity by activating NF-KB inflammatory pathway and P53 apoptosis pathway in zebrafish. *Toxicol Lett*. 2019;306:66-79.](#)
10. [Xia XH, Yuan YY, Liu M. The assessment of the chronic hepatotoxicity induced by Polygoni Multiflori Radix in rats: A pilot study by using untargeted metabolomics method. *J Ethnopharmacol*. 2017;203:182-90.](#)
11. [Li A, Gao M, Zhao N, Li P, Zhu J, Li W. Acute liver failure associated with Fructus Psoraleae: a case report and literature review. *BMC Complement Altern Med*. 2019;19\(1\):84.](#)
12. [Zhou W, Chen X, Zhao G, Xu D, Jiang Z, Zhang L, et al. Psoralen Induced Liver Injury by Attenuating Liver Regenerative Capability. *Front Pharmacol*. 2018;9:1179.](#)
13. [Gong X, Liu M, Gong L, Li Y, Peng C. Study on hepatotoxicity of different dosages of Polygoni multiflori radix praeparata in rats by metabolomics based on UPLC-Q-TOF-MS. *J Pharm Biomed Anal*. 2019;175:112760.](#)
14. [Reddy S, Mishra P, Qureshi S, Nair S, Straker T. Hepatotoxicity due to red bush tea consumption: a case report. *J Clin Anesth*. 2016;35:96-98.](#)

15. [Becker MW, Lourençone EMS, De Mello AF, Branco A, Filho EMR, Blatt CR, et al. Liver transplantation and the use of KAVA: Case report. *Phytomedicine*. 2019;56:21-26.](#)
16. [Ruperti-Repilado FJ, Haefliger S, Rehm S, Zweier M, Rentsch KM, Blum J, et al. Danger of Herbal Tea: A Case of Acute Cholestatic Hepatitis Due to *Artemisia annua* Tea. *Front Med \(Lausanne\)*. 2019;6:221.](#)
17. [Liu DM, Yang D, Zhou CY, Wu JS, Zhang GL, Wang P, et al. Aloe-emodin induces hepatotoxicity by the inhibition of multidrug resistance protein 2. *Phytomedicine*. 2020;68:153148.](#)
18. [Fan Q, Zhao B, Wang C, Zhang J, Wu J, Wang T, et al. Subchronic Toxicity Studies of Cortex Dictamni Extracts in Mice and Its Potential Hepatotoxicity Mechanisms in Vitro. *Molecules*. 2018;23\(10\):2486.](#)
19. [Jia Z, Zhao C, Wang M, Zhao X, Zhang W, Han T, et al. Hepatotoxicity assessment of Rhizoma Paridis in adult zebrafish through proteomes and metabolome. *Biomed Pharmacother*. 2020;121:109558.](#)
20. [Costa ML, Rodrigues JA, Azevedo J, Vasconcelos V, Eiras E, Campos MG. Hepatotoxicity induced by paclitaxel interaction with turmeric in association with a microcystin from a contaminated dietary supplement. *Toxicol*. 2018;150:207-11.](#)
21. [Cachet X, Langrand J, Riffault-Valois L, Bouzidi C, Colas C, Dugay A, et al. Clerodane furanoditerpenoids as the probable cause of toxic hepatitis induced by *Tinospora crispa*. *Sci Rep*. 2018;8\(1\):13520.](#)
22. [Corey R, Werner KT, Singer A, Moss A, Smith M, Noelting J, et al. Acute liver failure associated with *Garcinia cambogia* use. *Ann Hepatol*. 2016;15\(1\):123-6.](#)
23. Wang YL. A case report on chronic arsenic poisoning caused by long-term taking Niu Huang Jiedu Pian. *China Occupational Med*. 2007;3:258.
24. [Yang L, Guo XX, Song HB. Hepatic Lesion Risk Analysis of Yangxueshengfa Capsule. *Chin J Pharmacovigilance*. 2013;10\(06\):362-5.](#)
25. [Dong X, Fu J, Yin X, Cao S, Li X, Lin L, et al. Emodin: A Review of its Pharmacology, Toxicity and Pharmacokinetics. *Phytother Res*. 2016;30\(8\):1207-18.](#)
26. [Jin C, Wu Z, Wang L, Kanai Y, He X. CYP450s-Activity Relations of Celastrol to Interact with Triptolide Reveal the Reasons of Hepatotoxicity of *Tripterygium wilfordii*. *Molecules*. 2019;24\(11\):2162.](#)
27. [Zhou W, Chen X, Zhao G, Xu D, Jiang Z, Zhang L, et al. Psoralen Induced Liver Injury by Attenuating Liver Regenerative Capability. *Front Pharmacol*. 2018;9:1179.](#)
28. Chen X, Wang DG, Feng ZP, Li JX, Zhang GY, Liu ZC, et al. Establishment of a new method of processing *Aconiti Lateralis Radix Praeparata* based on Sini Decoction. *Chin Trad Patent Med*. 2020;42(5):1255-61.
29. [Li A, Gao M, Zhao N, Li P, Zhu J, Li W. Acute liver failure associated with *Fructus Psoraleae*: a case report and literature review. *BMC Complement Altern Med*. 2019;19\(1\):84.](#)
30. [Zhuang T, Gu X, Zhou N, Ding L, Yang L, Zhou M. Hepatoprotection and hepatotoxicity of Chinese herb Rhubarb \(*Dahuang*\): How to properly control the "General \(Jiang Jun\)" in Chinese medical herb. *Biomed Pharmacother*. 2020;127:1110224.](#)

31. [Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, et al. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg. 2003;138\(8\):852-8.](#)
32. [Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. Lancet. 1992;340\(8820\):674.](#)
33. [Kao WF, Hung DZ, Tsai WJ, Lin KP, Deng JF. Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. Hum Exp Toxicol. 1992;11\(6\):480-7.](#)
34. [Gandhi D, Ahuja K, Quade A, Batts KP, Patel L. Kratom induced severe cholestatic liver injury histologically mimicking primary biliary cholangitis: A case report. World J Hepatol. 2020;12\(10\):863-9.](#)
35. [Corey R, Werner KT, Singer A, Moss A, Smith M, Noelting J, et al. Acute liver failure associated with *Garcinia cambogia* use. Ann Hepatol. 2016;15\(1\):123-6.](#)
36. [Xiong F, Guan YS. Cautiously using natural medicine to treat liver problems. World J Gastroenterol. 2017;23\(19\):3388-95.](#)
37. [Li YX, Gong XH, Liu MC, Peng C, Li P, Wang YT. Investigation of Liver Injury of *Polygonum multiflorum* Thunb. in Rats by Metabolomics and Traditional Approaches. Front Pharmacol. 2017;8:791.](#)
38. [Miao YY, Luo L, Shu T, Wang H, Jiang ZZ, Zhang LY. Study on difference of liver toxicity and its molecular mechanisms caused by *Tripterygium wilfordii* multiglycoside and equivalent amount of triptolid in rats. Zhongguo Zhong Yao Za Zhi. 2019;44\(16\):3468-77.](#)
39. [Liu J, Zhao Y, Xia J, Qiu M. Matrine induces toxicity in mouse liver cells through an ROS-dependent mechanism. Res Vet Sci. 2020;132:308-11.](#)
40. [Hackbarth H. Possibilities and limits of the inspection of animal experiments and laboratory animal facilities. Dtsch Tierarztl Wochenschr. 2002;109\(3\):109-11.](#)
41. [Wang Y, Feng F. Evaluation of the Hepatotoxicity of the Zhi-Zi-Hou-Po Decoction by Combining UPLC-Q-Exactive-MS-Based Metabolomics and HPLC-MS/MS-Based Geniposide Tissue Distribution. Molecules. 2019;24\(3\):511.](#)
42. [Tu C, Niu M, Li C, Liu Z, He Q, Li R, et al. Network pharmacology oriented study reveals inflammatory state-dependent dietary supplement hepatotoxicity responses in normal and diseased rats. Food Funct. 2019;10\(6\):3477-90.](#)
43. [Tao Y, Wang R, Lai Q, Wu M, Wang Y, Jiang X, et al. Targeting of DDR1 with antibody-drug conjugates has antitumor effects in a mouse model of colon carcinoma. Mol Oncol. 2019;13\(9\):1855-73.](#)
44. [DeKlotz CMC, Roby KD, Friedlander SF. Dietary Supplements, Isotretinoin, and Liver Toxicity in Adolescents: A Retrospective Case Series. Pediatrics. 2017;140\(4\):20152940.](#)
45. [Melchardt T, Magnes T, Weiss L, Grundbichler M, Strasser M, Hufnagl C, et al. Liver toxicity during temozolomide chemotherapy caused by Chinese herbs. BMC Complement Altern Med. 2014;14:115.](#)
46. [Costa ML, Rodrigues JA, Azevedo J, Vasconcelos V, Eiras E, Campos MG. Hepatotoxicity induced by paclitaxel interaction with turmeric in association with a microcystin from a contaminated dietary supplement. Toxicon. 2018;150:207-11.](#)

47. [Expert Committee on Clinical Application of Glycyrrhizin Preparation in the Treatment of Liver Diseases. J Clin Hepatol. 2016;32\(05\):844-52.](#)
48. Miao SH, Gao JS. Research Progress on Pharmacological Effect of Curcumin. *Guangming J Chin Medicine*. 2017;32(15):2284-7.
49. Jin QX. Analysis of Soluble Sulphur and Mercury Contents in Cinnabar Prepared by Elutriation. *Chin J Ration Drug Use*. 2017;14(03):12-14.
50. Shi RJ, Wu H, Yu HL, Chen L. The research of ginger detoxification to Pinellia ternate—anti-inflammatory effect of ginger on inflammation induced by raphides in pinellia ternate. *Pharmacol Clin Chin Materia Medica*. 2010;26(04):42-44.

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